example of the second-generation neonicotinoids. CGA 293′343 provides excellent control of sucking and chewing insects. Control of most insect pests with CGA 293′343 is superior or equivalent to that of currently registered neonicotinoid insecticides. Structure–activity relationships revealed that variation of the pharmacophore, the oxadiazinane ring, the heterocylcic group and the substituent R in CGA 293′343 diminish biological activity against *Aphis craccivora*.

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Synthetic approaches towards CGA 293'343: A novel broad-spectrum insecticide

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Abstract: Synthetic approaches towards CGA 293'343 (ISO draft common name: thiamethoxam), a novel broad-spectrum insecticide from the class neonicotinoids, are described. 2-Chloro-5-chloromethylthiazole, an important synthetic intermediate, was prepared from five different precursors. Alternatively, CGA 293'343 was prepared via the intermediate 2-benzylmercapto-5-chloromethylthiazole, the synthesis of which is also described.

Keywords: CGA 293'343; thiamethoxam; neonicotinoid; insecticide; thiazole; oxadiazinane; synthesis

1 INTRODUCTION

CGA 293'343[1] (Fig 1; ISO draft common name: thiamethoxam), which is a novel broad-spectrum insecticide, shows outstanding activity against a wide spectrum of important pests; it belongs to the class of neonicotinoids[2] and is currently under worldwide development by Novartis Crop Protection. In the course of development, the need for a practical and economically viable synthesis arose.

One synthesis of CGA 293'343 utilises the route shown in Fig 1. Reaction of 2-chloro-5-chloromethylthiazole **2** with the oxadiazinane intermediate **1** gave the desired product in good yield. Therefore, the core task to be addressed in the synthesis plan was the construction of the chlorothiazole moiety.

To date, apart from our work, five synthetic routes for compound **2** have been published. When we started out on our endeavour, only two references[3,4] were known. Neither route satisfied our need for a high-yielding, economically and ecologically sound process. After completion of our synthetic studies, further synthetic routes[6–8] were subsequently

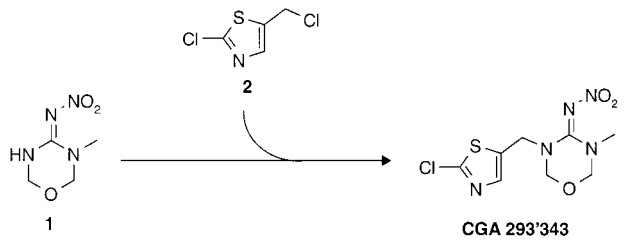

Figure 1. Synthesis of CGA 293'343 from the intermediate **2**. Reaction conditions: DMF, K_2CO_3, 2 h, 60°C, 74%.

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published, of which those in References 5 and 8 overlapped with our own, independent work.

2 SYNTHETIC ROUTES

*2.1 2-Chloro-5-chloromethylthiazole (**2**; Fig 1).* We followed two synthetic approaches, which are shown in Fig 2. Compounds **4**, **5** and **6** are acyclic precursors with the functionality set up in such a way that, after cyclisation, the 2-chloro- and the 5-chloromethyl group are formed. In contrast, precursors **8** and **10** already possess the proper heterocyclic ring skeleton; conversion to **2** then proceeds in one step. Note that for compound **8** this means (i) replacement of the sulfur substituent by chlorine, and (ii) transformation of the exomethylene group into a chloromethyl group, both processes accompanied by a double bond shift leading to aromatisation. In the next section, another synthetic strategy will be discussed, in which the modifications (i) and (ii) are conducted in two separate steps.

The sodium salt **4** was prepared from the previously described amine **3** and carbon disulfide.[9] Oxidation with iodine or hydrogen peroxide gave the disulfide, which, on treatment with sulfuryl chloride, cyclised to give **2**.[10] The isonitrile **6** was prepared from the corresponding formamide **5** by treatment with a dehydrating agent such as thionyl chloride ($SOCl_2$). With SCl_2, the isonitrile **6** cyclised to form **2**.[11] This process could also be performed in one step by addition of $SOCl_2$ and SCl_2 to the formamide **5**.

The thiazole **10**, prepared from the commercially available aminothiazole **9** via a Sandmeyer reaction, could be halogenated on the methyl group with NCS to give **2**.[10] Use of *N*-bromosuccinimide (NBS) gave 5-bromomethyl-2-chlorothiazole, which is also a useful intermediate for the synthesis of CGA 293'343. The previously described thiothiazole **8** was prepared in high yield from **7** and CS_2.[12] Treatment of 8 with chlorine or sulfuryl chloride gave **2**.[10]

*2.2 The intermediate 2-benzylmercapto-5-chloromethylthiazole **12**.* Synthesis of **2** from precursor **12** represents a third synthetic strategy, as shown in Fig. 3. Compound **12** has a chloromethyl group already in place, and the benzylmercapto substituent can be exchanged for chlorine. This can be done directly, leading to **2**, or after attachment to the oxadiazinane intermediate **1**, opening up an alternative reaction scheme as shown in Fig 4. As demonstrated in Fig 3, the intermediate **12** can be prepared by a variety of methods.

The commercially available mercaptothiazole **13** was alkylated to give 2-benzylmercaptothiazole **14**. The intermediate **12** was prepared by treatment of **14** with $DMF/POCl_3$, subsequent catalytic hydrogenation of the product **15**, and treatment of the resulting alcohol with $SOCl_2$.[13] **12** was then chlorin-

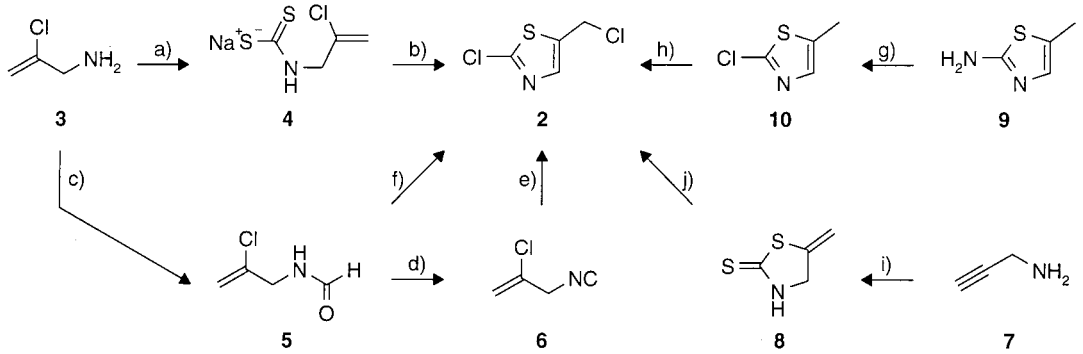

Figure 2. Synthesis of intermediate **2**: a) H_2O, NaOH, CS_2, 85%, b) H_2O, KI, I_2, then CH_2Cl_2, SO_2Cl_2, 30%, c) $HCO_2C_2H_5$, reflux, 12 h, 90%, d) DMF, $SOCl_2$, Na_2CO_3, 12 h, 80%, e) CCl_4, SCl_2, 40°C, 4 h, 50%, f) $SOCl_2$, SCl_2, reflux, 24 h, 42%, g) t-BuONO, $CuCl_2$, CH_3CN, 60%, h) *N*-chlorosuccinimide, dibenzoylperoxide, CCl_4, reflux, 50%, i) CS_2, EtOH, ambient temperature, 2 h, 90%), j) CH_2Cl_2, H_2O, SO_2Cl_2, 1 h, 80%.

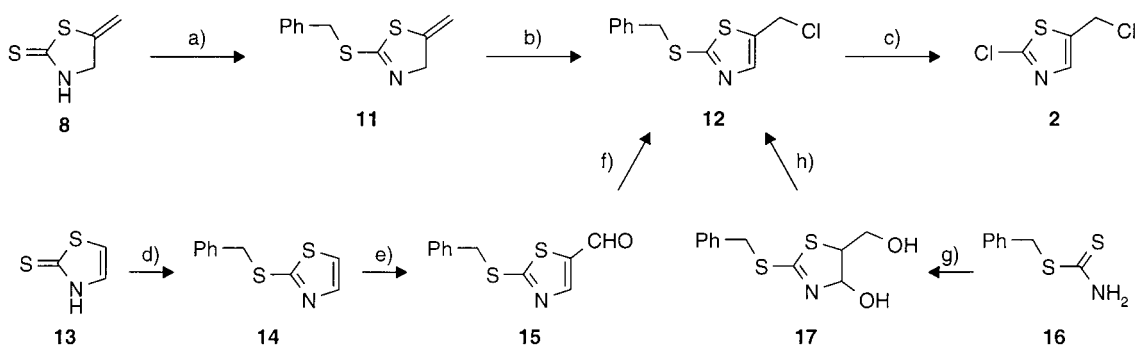

Figure 3. Synthesis via the intermediate **12**: a) CH_3CN, K_2CO_3, benzylbromide, 60°C, 1 h, 70%, b) CH_2Cl_2, $NaHCO_3$, SO_2Cl_2, 60%, c) CH_2Cl_2, 2 h, 60%, d) CH_3CN, K_2CO_3, benzylbromide, 60°C, 1 h, 80%, e) DMF, $POCl_3$, 40°C, 6 h, 35%, f) H_2, PtO_2, $FeCl_2 \cdot 4\,H_2O$, ethyl acetate, then $SOCl_2$, CH_2Cl_2, 3 h, 60%, g) ethanol, H_2O, glycidyl aldehyde, 12 h, 85%, h) CH_2Cl_2, $SOCl_2$, 3 h, 90%.

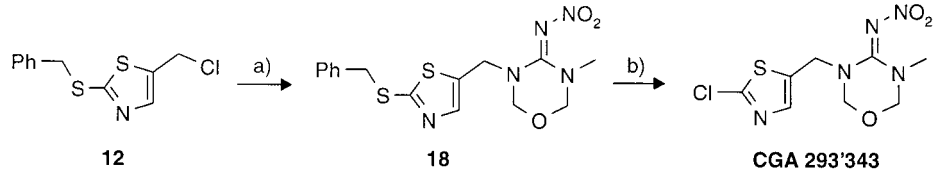

Figure 4. Alternative synthesis of CGA 293'343 from the intermediate **12**. Reaction conditions: a) oxadiazinane **1**, DMF, K_2CO_3, 2 h, 60°C, 75%, b) HCl, H_2O, C_6H_5Cl, Cl_2, 6 h, 80%.

ated to give **2**. Another synthetic approach to **12** is chlorination of 2-benzylmercapto-5-methylene-thiazoline **11**,[14] which is available by alkylation of **8** with benzylbromide. **12** was also prepared by treatment of diol **17** with $SOCl_2$.[13] Diol **17** was constructed from the previously described dithiocarbamate **16** by reaction with glycidyl aldehyde.[15]

An alternative synthesis is shown in Fig 4. Coupling of **12** with **1** followed by chlorination of the intermediate **18** gave CGA 293'343.[13]

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Non-steroidal ecdysone agonists: New tools for IPM and insect resistance management

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Abstract: The non-steroidal, bis-acylhydrazine agonists of the insect molting hormone, 20-hydroxyecdysone, were first discovered over ten years ago. An extensive structure–activity optimization program yielded one commercial insecticide, tebufenozide (RH-5992) and two additional candidate insecticides (methoxyfenozide and halofenozide) which are in development. Tebufenozide is highly selective for lepidopteran pest control and is thus useful for IPM and resistance management programs. Methoxyfenozide (RH-2485) is also lepidopteran-selective but significantly more potent than tebufenozide and offers control of a wider range of lepidopteran pests. Halofenozide (RH-0345) is generally less potent and selective than tebufenozide or methoxyfenozide. However, its physical and biological properties make it well suited for control of beetle grubs and caterpillars in the soil. Target pest selectivity, new and novel mode of action, ecotoxicological safety and safety to beneficial arthropods make these insecticides valuable tools for integrated pest and resistance management programs.

Keywords: tebufenozide; methoxyfenozide; halofenozide; ecdysone agonists; RH-5992; RH-2485; RH-0345; IPM; resistance management programs

The steroid insect moulting hormone, 20-hydroxyecdysone (20E), and the sesquiterpenoid juvenile hormone play a central role in the regulation of the growth and development, as well as of reproductive processes, in insects. As such, chemicals which mimic or antagonize the action of these two hormones have been sought for use as safe, third-generation pesticides. While success in the discovery of juvenile hormone mimetics came much earlier,[1] it is only recently that insecticides which act as agonists of 20E have been discovered.[2]

Scientists at Rohm and Haas Company have discovered three non-steroidal ecdysone agonists, all of which belong to bis-acylhydrazine chemistry.[2] One of these, *N-tert*-butyl-*N'*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide (tebufenozide; RH5992) was the first to be commercialized as a leptidopteran-specific insecticide under the trade names Mimic®, Confirm® and Romdan® in several countries.

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